Genetic Studies in Holoprosencephaly as a Model to Study Forebrain Development

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Holoprosencephaly (HPE) is a congenital malformation of the brain that is common in live births (1:16,000) and even more common among spontaneous abortions (1:250). The basic anomalies in HPE involve an abnormal development of the forebrain and often the face (1). Although teratogens such as maternal diabetes are known to be associated with HPE, genetic causes are well-documented and include non-random chromosome anomalies in HPE, familial occurrence of HPE, and known genetics syndromes or associations with HPE. Cytogenetic anomalies consist of deletions or duplications of at least eleven chromosomal regions including 13q, del(18p), del(7)(q36), dup(3) (p24-pter), del(2)(p21) and del(21)(q22.3). Several of these chromosomal regions have been shown to carry genes that are crucial for normal forebrain development and, when altered, lead to the clinical and pathological findings of HPE.

The first gene identified, and probably the most important one in contributing to HPE, is the embryonic patterning gene, *Sonic Hedgehog (SHH)* located in 7q36 (2). Loss-of-function mutations in *SHH* have been shown to cause sporadic and up to 37% of familial HPE (2,3). To become the active morphogen, the SHH protein undergoes autoprocessing and covalent linkage to cholesterol suggesting that decreased or absent levels of cholesterol may be involved in the etiology of HPE (for review see 1). Thus, it is not surprising that HPE can be part of the Smith-Lemli-Opitz syndrome that is associated with a defect of cholesterol biosynthesis (4). The clinical findings in individuals with *SHH* mutations are extremely variable. They may include alobar, semilobar, lobar HPE, cyclopia, ethmocephaly, cebocephaly, premaxillary agenesis, clefting of lip and/or palate, ocular coloboma, congenital nasal pyriform aperture stenosis (CNPAS), single central incisor (SCI), mild to severe developmental delay/mental retardation, attention deficit/hyperactivity (ADHD) (5), and normal IQ in phenotypically normal mutation carriers. SHH mutations have also been identified in individuals without HPE, but HPE microsigns: SCI (6), ocular coloboma (7), but not in patients with cleft lip and/or palate (8).

In addition to *SHH*, heterozygous mutations were identified in *ZIC2*, a homologue to the *Drosophila odd-paired* gene, which is located in 13q32 (9,10). Furthermore, the *SIX3* gene, a homologue to the *sine oculis/optix* gene, was identified in 2p21 (11). Loss-of-function mutations in the TG-interacting factor (TGIF) gene have been shown to cause HPE (12). Interestingly, TGIF connects the Nodal/TGF-beta and the Hedgehog signaling pathways both of which are crucial for early human embryonic development. A systematic mutation screen of genes in either the SHH or Nodal/TGF-beta signaling pathways is in progress and has shown PATCHED (PTCH1) (13) and CRYPTO (TDGF1) (14) is mutated in patients with HPE or other forebrain defects.

Identification of these and additional genes involved in HPE will allow a detailed comparison of expression, function, and possible interactions of these genes. This analysis will also shed light on the normal development of the forebrain and midface. Furthermore, it will elucidate the basic mechanism(s) of abnormal development and the extreme variability of the phenotypic expression as seen in holoprosencephaly.

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Review:

Muenke, M., Beachy, P.A.: Holoprosencephaly. Chapter 250 in volume 4: Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D., Childs, B., Kinzler, K.W., Vogelstein, B. (eds.) "The Metabolic and Molecular Bases of Inherited Disease". McGraw-Hill Companies, Inc., Eighth Edition pp. 6203-6230, 2001

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